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STUDY PROTOCOL

The Japanese Pediatric Continuous Renal Replacement Therapy (jpCRRT) Registry: Study Protocol

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ABSTRACT

BACKGROUND

The use of continuous renal replacement therapy (CRRT) in critically ill children is rapidly increasing, but the standard of care has not yet been established and prognosis remains poor. To develop optimal CRRT strategies, we launched a research project generating the Japanese Pediatric CRRT registry, a multicenter registry of CRRT in Japanese pediatric intensive care units (PICUs), to investigate the actual status of CRRT in recent years in PICUs, where data are lacking.

METHODS

This manuscript presents a protocol for planning a multicenter prospective registry. As of April 2023, 15 Japanese PICUs are voluntarily participating. Patients enrolled are those <16 years of age who enter the PICUs of the collaborating institutions, require CRRT, and have the guardians' consent. CRRT is defined as anticipated to be required for >24 hours, and CRRT connected to extracorporeal membrane oxygenation is also included. The registry is an online registry system managed by the University Hospital Medical Information Network. The primary outcomes are Pediatric Cerebral Performance Category Scale at PICU discharge and 6 months post-discharge (deaths included), persistent need for dialysis, and PICU readmission within 6 months. The secondary outcomes are adverse events during and immediately after CRRT initiation, and initial circuit life span.

CONCLUSIONS

This project will examine the differences in outcomes of CRRT in PICUs in specific patient and treatment groups and will be used to design future interventional studies. We will also aim to establish a platform for a multicenter registry study in Japanese PICUs, considering the current lack of such a platform.

KEY WORDS

Kidney Replacement Therapy, Cohort Studies, Pediatric, Nafamostat, Japan

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INTRODUCTION

Continuous renal replacement therapy (CRRT) is a common treatment option for critically ill pediatric patients [1]. However, the prognosis for these patients remains poor, with the proportion of deaths in the pediatric intensive care units (PICUs) ranging from 30 to 40% [2–4]. In particular, patients who have undergone blood stem cell transplantation or who have multiple organ failure have an even higher proportion of deaths, reportedly 52–65% [5] and 43–92% [6–8], respectively. Despite the urgent need to improve outcomes for these patients, the lack of evidence has prevented the establishment of standardized treatment strategies. This is in part due to the complexity of CRRT, which comprises various treatment options that can be challenging to optimize for each patient.

Understanding the actual practice of CRRT in the PICU is essential for the development of effective treatments. Unfortunately, recent multicenter reports on the actual practice of CRRT for patients in PICUs are scarce. The Prospective Pediatric CRRT registry, the largest multicenter registry in PICUs, has data on 370 patients from 13 United States centers, from 2001 to 2005 [10]. The registry has provided some information, including that the groups with the highest proportion of deaths are patients with multiorgan dysfunction syndrome [6] and stem cell transplant recipients [11]. Fluid overload was also identified as an independent risk factor for mortality [12]. However, because standardized treatment strategies have not yet been established, further research is needed.

To address the lack of evidence regarding CRRT practices, the Japanese Pediatric CRRT (jpCRRT) registry was designed to investigate the actual practice of CRRT patients in Japanese PICUs. The registry has three main objectives: 1) investigate the characteristics of patients who require CRRT in Japanese PICUs and describe the differences in outcomes in specific patient groups, 2) determine the actual practice of CRRT in Japanese PICUs and investigate differences in outcomes for each treatment choice, and 3) identify new clinical issues that may lead to the planning of randomized controlled trials. A questionnaire survey of PICU directors in 2022 prior to this registry revealed a wide variety of treatment strategies implemented in Japanese PICUs, including some that are considered unique to Japan (e.g., nafamostat mesylate is frequently selected as an anticoagulant) and others that are new to the field, such as rehabilitation during CRRT [13]. The registry is significant because pediatric CRRT practices in Japan differ significantly from those in the rest of the world. Thus, comparing outcomes by practice is crucial for identifying effective treatments. The registry also includes items aimed at examining new clinical issues that have not been focused on in previous studies. By addressing the lack of evidence, the jpCRRT registry has the potential to improve the prognosis of CRRT patients in the PICU.

METHODS

STUDY DESIGN

This manuscript is a protocol for planning a multicenter prospective registry, named the jpCRRT registry. All PICUs in Japan (36 institutions as of 2022) were recruited via a mailing list to which all PICU representatives in Japan subscribed, and 15 institutions (42% of all Japanese PICUs) are voluntarily participating (**Fig. 1**). The institutions with PICUs are limited to university hospitals, children's hospitals, and regional tertiary care centers. Recruitment is ongoing, and the number of participating institutions may increase in the future.

PARTICIPANTS

Participants in the jpCRRT registry are all patients under 16 years of age admitted to the PICUs of the collaborating centers who require CRRT and for whom guardian consent is obtained. Those who require CRRT connected to extracorporeal membrane oxygenation (ECMO) are also included. Patients scheduled to be admitted for maintenance dialysis are excluded. Although enrollment in the jpCRRT registry began on January 1, 2023, the actual start of enrollment of patients at each collaborating institution did not necessarily coincide with the start of enrollment at each institution, since enrollment of participants begins once the study has been approved by the ethical review committee for each institution independently.

STUDY SIZE AND FEASIBILITY

To ensure that enough cases are included in our registry study, we aim to exceed the 370 cases enrolled in similar multicenter pediatric CRRT registries in the past, although it is challenging to set a specific target. Based on the results of the preliminary survey and the number of participating sites, we anticipate enrolling around 100 cases annually, totaling approximately 500 cases over a 5-year period. The study will analyze subgroups such as combined ECMO cases, neonates, sepsis, congenital heart disease, and metabolic disorders. However, the number of cases needed for these analyses may increase.

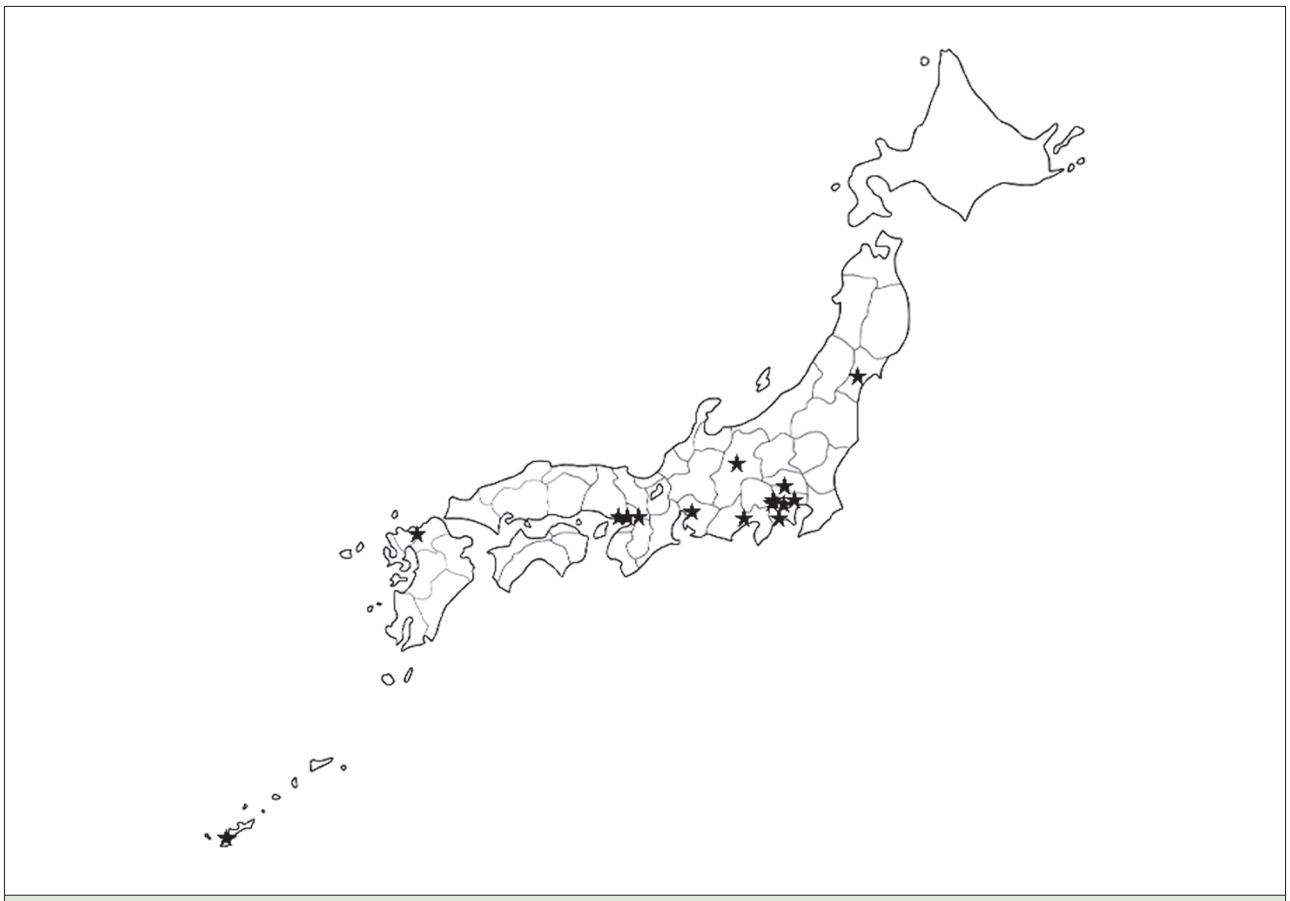

Fig. 1 **Location of the 15 PICUs participating in the jpCRRT registry**
PICU, pediatric intensive care unit; jpCRRT, Japanese pediatric continuous renal replacement therapy

The enrollment period for the jpCRRT registry is expected to be around 5 years but may be shortened or extended based on enrollment numbers and funding availability.

ETHICAL APPROVAL

First, the Ethical Review Committee of Osaka City General Hospital, the lead institution in this study, has provided ethical approval for registry enrollment (reference number: 2210069). Each collaborating institution must obtain ethical approval from its corresponding ethical review committee before it can begin enrollment in the jpCRRT registry. In addition, it is mandatory to obtain a completed study participation consent form from the parents or guardians.

PRIVACY PROTECTION AND REGISTRY SYSTEM

Data registered in the jpCRRT registry is anonymized information that cannot be used to identify individuals. Participants are assigned a study-specific ID, to be used as the participants' identifier. The correspondence list between the study-specific ID and the electronic medical record number will be kept in lockable storage under the supervision of the Clinical Trial Management Office at each research site to ensure that confidentiality is adequately ensured. When the results of the study are made public, it is strictly prohibited to include any personal information of the participants. We will not use the information obtained about participants for any purpose other than that of the research.

The jpCRRT registry uses the Internet Data and Information system for Clinical and Epidemiological research, Cloud version (INDICE cloud), managed by University Hospital Medical Information Network. The information system is secured by personal authentication IDs and passwords, with 128 Bit SSL encryption and VPN, double firewalls, and a monitoring system for unauthorized access and prohibition of intrusion. In addition, monitoring of physical equipment includes access control using vein authentication and installation of surveillance cameras.

DATA MANAGEMENT AND QUALITY CONTROL

To prevent the entry of improbable data, we limited the types and scope of data that can be entered. Additionally, to prevent data entry omissions, the registration cannot be completed until all items have been entered. If the data are unknown, we input "unknown". Furthermore, the jpCRRT registry administration office monitors the registered data every 2 months, and if any abnormal data input is suspected, the person who entered the data would be contacted, to maintain data quality.

DATA COLLECTION

This is an exploratory study to understand the actual situation of CRRT in Japanese PICUs, as described above, and substantial data will be collected over time. When CRRT is initiated in the PICU, consent is obtained if the patient meets the inclusion criteria. After consent is obtained, data will be collected at the following three time points: at the time of first circuit replacement/termination, at the time of PICU discharge, and 6 months after PICU discharge.

VARIABLES

Detailed definitions of each variable are provided in the **Supplementary Table**. The registry items are to be reviewed once a year, which may result in deletions, additions, or amendments to the registry items if agreed on by more than 2/3 of the Steering Committee.

OUTCOMES

Primary outcomes include the Pediatric Cerebral Performance Category Scale (deaths included) [14], dialysis demand at PICU discharge and 6 months later, as well as whether the patient is readmitted to the PICU within 6 months of PICU discharge. Secondary outcomes are adverse events during and immediately after CRRT initiation, and initial circuit life span.

COVARIATES

Patient background data include sex, height, weight, date and time of admission to the PICU, reason for admission to the PICU (and surgical classification if admission was postoperative), underlying disease, maintenance dialysis state, serum creatinine level before the condition worsened, post-tracheostomy status, use of a home ventilator, predicted mortality at PICU admission (Pediatric Index of Mortality 3) [15], and organ failure score (pediatric Sequential Organ Failure Assessment) [16]. Information collected at the time of CRRT induction includes date and time of CRRT initiation, indicated CRRT condition, blood access (size and site), presence of concomitant extracorporeal membrane oxygenation, urine output before CRRT induction, blood test values immediately before CRRT induction (e.g., serum creatinine, urea nitrogen), vital signs (e.g., blood pressure, heart rate), respiratory support, and inotropic dosage. Initial blood circuit information includes the priming capacity of the circuit, modality, type and surface area of hemofilter, blood priming (type and volume of blood products used), presence of pre-dialysis prior to patient connection, adverse events immediately after patient connection, CRRT settings (e.g., blood flow), time to first circuit exchange, reason for exchange, used anticoagulants, and anticoagulation monitoring methods. CRRT-related information to be collected at PICU discharge includes adverse events during CRRT use (e.g., intracranial hemorrhage, catheter-related blood stream infection), rehabilitation during CRRT, use of analgesics and sedatives, target sedation level (assessed with the Richmond Agitation-Sedation Scale) [17], and total number of CRRT days performed.

STATISTICAL ANALYSIS

The following statistical methods will be used in future analysis of data from this registry. Descriptive statistics will be reported for patient baseline characteristics, CRRT initiation and initial circuit information, and outcome variables. Continuous variables will be expressed as medians with interquartile ranges, whereas categorical variables will be expressed as frequencies and percentages. Group comparisons will be made for each outcome category to identify potential confounders. The appropriate statistical method will be selected according to the number of comparison groups (e.g., the Wilcoxon rank-sum test for two-group comparisons of continuous variables). The Kaplan–Meier time-to-event analysis will be used to describe circuit life span, and survival curves will be compared between specific groups using the log-rank test. Multivariable regression analysis will be used to identify factors associated with outcomes, adjusting for potential confounders.

TEST REGISTRATION

To determine whether the registry could be operated without problems, a pilot registration of the jpCRRT registry was conducted at three facilities for 3 months prior to the study to identify problems in actual operation. The number of input items was adjusted, insufficient explanatory text and options were added, and system deficiencies were corrected. Within the limits of the

system's operability, changes have been made to minimize the time and effort required for data entry, and a format with easy data entry has been achieved.

CLINICAL ISSUES USING THIS REGISTRY

The registry is meaningful because pediatric CRRT practices (e.g., modalities, anticoagulants) differ significantly between Japan and the rest of the world [13], allowing for comparisons of outcomes by practice. The registry also includes items aimed at examining the following new clinical issues that have not been focused on in previous studies: (1) comparison of circuit lifespan between nafamostat (used only in Japan and Korea) and other anticoagulants, (2) association between circuit priming method (blood products used or not and type of blood products used) and adverse events/outcomes, (3) association between rehabilitation during CRRT and adverse events/outcomes, and (4) association between sedation medications, sedation goals and adverse events/outcomes during CRRT.

DISCUSSION

CONTRIBUTION

This project using the jpCRRT registry will investigate the recent status of CRRT for severely ill pediatric patients for whom data is lacking. Comparison of this registry data with previous Japanese data and available foreign data will allow us to examine the impact of different treatment options on outcomes and may lead to the establishment of optimal CRRT treatment strategies. However, since this study is only an observational study, comparison of interventions in studies such as randomized controlled trials, will be necessary to evaluate the superiority or inferiority of each treatment option. In addition, the groundwork for a multicenter registry study in Japanese PICUs is yet to be established. If this project is successful, we hope to use this registry system as a platform for the development of multicenter registry studies in Japanese PICUs, either by adapting the registry system to other diseases and treatments or by encompassing multiple diseases.

LIMITATIONS

There are several limitations to this registry study. The first is selection bias. As participation in this study is voluntary rather than mandatory, it is likely that a higher proportion of sites with a strong commitment to clinical research or to CRRT will tend to participate. In addition, because this study includes only PICUs, information on CRRT performed outside of PICUs is excluded. In other words, since PICUs are only established in large hospitals in urban areas, the actual situation in small rural facilities will not be ascertained. In Japan, PICUs are being established throughout the country to enhance the care of critically ill pediatric patients (the number of PICU facilities has increased from 16 in 2013 to 36 in 2023). Even in 2008, when PICUs were not well established, many pediatric patients (84.1%) requiring acute blood purification were treated in ICUs [18], and it is estimated that an even higher percentage of patients are being treated in PICUs in recent years as PICUs have become more widespread throughout the country; therefore, the effect of this trend will likely be minimal. The second limitation is information bias. In this study, data entry into the registry is done by the researchers themselves via web registration, and the possibility of input errors cannot be ruled out. Measures to prevent improbable data entry are described in the data management and quality control subsection of the Methods section. Finally, the third limitation is the generalizability. Although this study is based on a population of critically ill pediatric patients who require CRRT, there are potential racial and cultural differences, as well as CRRT practice methods unique to Japan that may prevent generalizability to other countries. For example, an international cross-sectional study on acute blood purification in adults reported the following three particularities of Japan: 1) low CRRT treatment doses due to insurance approval restrictions, 2) adsorption by hemodiafiltration membranes rather than high-flow hemofiltration is indicated for sepsis, and 3) nafamostat mesylate is widely used as an anticoagulant, while sodium citrate is rarely used [19]. Our questionnaire survey also showed that diffusion therapy was preferred in Japanese PICUs and nafamostat mesylate was used more frequently as an anticoagulant compared to the use in North America and Europe [13]. While these Japanese peculiarities may hinder generalizability, they may also lead to the discovery of research areas that are difficult to conduct only in Japan.

CONCLUSION

This paper presents the objectives and contents of the project using the jpCRRT registry, a multicenter registry in the Japanese PICU. The data available in this registry will supplement missing information on recent CRRT practices for children and be useful in establishing standard CRRT treatment strategies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest in relation to the work presented in the manuscript.

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